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EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/060,738	LIN ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 2-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/2/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): The specification recites nucleic acid sequence on page 16, but no sequence listing or CRF is on file, and the sequences do not have proper sequence identifiers.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit a new CRF and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Objections

2. Claim 16 is objected to because of the following informalities: in line 2 of part (a) of claim 16, the it appears that the word "source" was left out of the claim when referring to "the first biological." Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite over the recitation "said known amount of said second nucleic acid used in step (a)" because step (a) recites a known amount of a second biological source containing a second nucleic acid but does not recite a known amount of a second nucleic acid. the claim is indefinite because it is not clear, therefore, if applicant intends that claim 1(a) recite a known amount of a second nucleic acid or if step (g) is meant to refer to the known amount of the second biological source containing the second nucleic acid. Claims 2-9 depend from claim 1 and are indefinite for this reason as well.

Claim 10 is indefinite over the recitation "said known amount of said second nucleic acid used in step (a)" because this phrase lacks proper antecedent basis in the claim. Step (a) of claim 10 recites a "known amount of cell culture system" but does not recite second nucleic acid or a known amount of second nucleic acid, in particular. Claims 11-15 depend from claim 10 and are indefinite for this reason as well.

In claim 14, the phrase "said extraction means" in line 2 lacks proper antecedent basis. While claim 10 recites a step of "extracting," it does not specifically recite an "extraction means."

Claim 15 is indefinite over the recitation "said first virus" and "said second virus" because claim 10, from which claim 15 depends, does not recite a first or second virus. Therefore, these phrases lack proper antecedent basis in the claims.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 1, 3, 4, 6, and 7 are rejected under 35 U.S.C. 102(a) as being anticipated by Kleiber *et al.* (Journal of Molecular Diagnostics, Vol. 2, No. 3, August 2000).

Kleiber *et al.* teach a method for the quantifying HCV RNA in a biological sample using the TaqMan principle in which signal is generated by cleaving two target-specific probes during amplification. Kleiber *et al.* teach a method for quantifying a first nucleic acid in a first biological source, comprising the steps of:

(a) combining said first biological source containing said first nucleic acid with a known amount of a second biological source containing a second nucleic acid (see p. 160, Specimen Preparation);

(b) extracting from said combination said first nucleic acid and said second nucleic acid to form a combined nucleic acid extract (see p. 160, Specimen Preparation);

(c) adding to said combined nucleic acid extract a first detectable probe which for said first nucleic acid and a second detectable probe which is specific for said second nucleic acid (p. 160, Reverse Transcription, Amplification, and Detection, first paragraph);

(d) amplifying said combined nucleic acid extract by PCR means with a first set of primers specific for said first nucleic acid and a second set of primers specific for said second nucleic acid (p. 160, Reverse Transcription, Amplification, and Detection, second paragraph);

(e) quantifying at various PCR cycles during said amplification a detectable signal released independently from said first detectable probe and said second detectable probe (p. 160, Reverse Transcription, Amplification, and Detection, third paragraph);

(f) extrapolating the results from step (e) to calculate the amount of said first nucleic acid in said first biological source and the amount of said second nucleic acid in said second biological source (p. 160, HCV RNA Quantitation); and

(g) evaluating accuracy of said calculated amount of said first nucleic acid determined by step (f) by comparing said calculated amount of said second nucleic acid in step (f) with said known amount of said second nucleic acid used in step (a) (p. 160, HCV RNA Quantitation).

In particular, HCV viral RNA was extracted using a buffer containing a known number of internal control (IC) molecules, a step which meets the limitations of (a) and (b) of claim 1. To the extracted sample, primers ST280 and ST778 are added, and two probes are added which are differentially labeled, one specific for HCV sequence and one for the internal control, as required by claims (c) and (d) of claim 1. The primers added by Kleiber *et al.* comprise many sets of primers which are specific for both the first and second nucleic acids. Kleiber *et al.* quantify the PCR at each cycle using the ABI Prism 7700 (limitation (e)), and extrapolate the amount of the HCV viral RNA and the IC nucleic acid based on the results of the quantification (limitation (f)). Kleiber *et al.* evaluate the accuracy of the calculated amount of the first nucleic acid by comparing said calculated amount with the amount of known IC nucleic acid, stating that samples with no detectable HCR RNA and negative IC result were reported as invalid (p. 160, last sentence). Thus, the teachings of Kleiber *et al.* meet the limitations of claim 1.

With regard to claims 3 and 4, Kleiber *et al.* the first biological source of Kleiber *et al.* is serum or plasma (p. 160).

With regard to claim 6, Kleiber *et al.* use RT-PCR (p. 160).

With regard to claim 7, any PCR mix inherently contains multiple "sets" of primers, as multiple copies of the forward and reverse primers are added to the PCR mix. The methods taught by Kleiber *et al.* therefore comprise the use of many sets of primers, wherein each set is specific to both the first and second nucleic acid.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleland *et al.* (Vox Sanguinis, 1999, 76: 170-174) in view of Gibson *et al.* (Genome Research, 1996, Vol. 6, No. 10, p. 995-1001).

Cleland *et al.* teach a method for amplification of Hepatitis C Virus (HCV) using Bovine Viral Diarrhoea Virus (BVDV) as an internal control. Cleland *et al.* teach that samples to be tested, such as plasma pools, were spiked with BVDV before extraction of RNA (p. 171, first column). Thus, Cleland *et al.* teach combining a first biological source containing a first nucleic acid with a second biological source containing a known amount of a second biological source containing a second nucleic acid (step (a) of claim 1) and extracting from said combination said first and second nucleic acids (step (b) of claim 1). Cleland *et al.* teach amplifying said combined nucleic acid extract by PCR with a set of primers specfic for each of the two nucleic acids (step (d) of claim 1; p. 171, second column). Cleland *et al.* suggest that a future development for their assay could include carrying out PCR "in the presence of labeled probes to allow the real-time detection of product during amplification. Differentiation between the internal control sequence from those of HCV or other test viruses could be achieved through the use of different labels for the BVDV and HCV probes (p. 174, final paragraph)," thus teaching step (c) of claim 1.

With regard to claim 3, Cleland *et al.* teach a first biological source plasma (p. 171).

With regard to claim 4, Cleland *et al.* teach the first nucleic acid is viral RNA (p. 171).

With regard to claim 5, Cleland *et al.* teach the second biological source cell-free BVDV (p. 171).

With regard to claim 6, Cleland *et al.* amplify using RT-PCR.

With regard to claim 7, Cleland *et al.* use sets of primers, one specific for HCV and one specific for BVDV (p. 171, Table 4).

With regard to claims 8 and 9, these claims recite an embodiment of claim 1 wherein the first nucleic acid is from HCV and the second is from BVDV. Cleland *et al.* teach a first biological sample containing HCV RNA and a second biological sample containing BVDV.

Cleland *et al.* do not teach using such a method to quantify amplification or extrapolate and evaluate amplification as required by steps (e), (f), and (g) of claim 1.

Gibson *et al.* teach a quantitative real-time RT-PCR method wherein two differentially labeled probes are included in an amplification tube and amplification is quantified at various PCR cycles via detectable signal relaxed independently from detectable probes. Gibson *et al.* exemplify the method via the use of a two-tube assay (one for the target probe and one for the control probe), but teach that assay throughput could be increased by adding both probes to the same RT-PCR tube using reporter dyes that are differentially detectable (step (e) of claim 1; p. 999, first column and p. 997). Finally, Gibson *et al.* evaluate the extrapolate the PCR results to determine the amount of starting nucleic acid and evaluate the accuracy of the method via comparison of the values determined during the quantitative PCR compared to the known amount of the second nucleic acid (steps (f) and (g) of claim 1; p. 997-998).

With regard to claim 2, Gibson *et al.* adjust the calculated amount of the first nucleic acid by a factor determined by comparing the calculated amount of the control with the known amount of the control (p. 997-998, figure 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Cleland *et al.* so as to have utilized

the quantification, extrapolation and evaluation methodologies taught by Gibson *et al.* One would have been motivated to have combined the two methods by Cleland's express guidance ot modify their methods to include the use of real time PCR and by Gibson *et al.*'s express teachings that the method they teach is "sensitive accurate and can be used to quantitate large numbers of samples in a relatively short time." Gibson *et al.* further teach that "The use of two different fluorescent hybridization probes and a known concentration of internal control RNA allows the initial mRNA copy number of an unknown target to be calculated (p. 999)." Therefore, in the absence of a secondary consideration, such as an unexpected result, the claimed invention is prima facie obvious.

10. Claims 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleland *et al.* (Vox Sanguinis, 1999, 76: 170-174) in view of Gibson *et al.* (Genome Research, 1996, Vol. 6, No. 10, p. 995-1001) as applied to claims 1-9 above, and further in view of Ladner *et al.* (Antimicrobial Agents and Chemotherapy, August 1997, p. 1715-1720).

Claims 10-16 are directed to methods for determining the effect of a compound on the replication of a first nucleic acid of a first biological source. As written, claim 10 is indefinite, but the claim appears to be an application of the method of claim 1 wherein the effect of a compound on the replication of a nucleic acid in the first biological sample is measured. The teachings of Cleland *et al.* in view of Gibson *et al.* are applied in this rejection as discussed previously, and address the limitations of steps (b)-(h) of claim 10, which specifically recite the steps of the quantification of nucleic acids.

With regard to claim 11, Cleland *et al.* teach cell-free hepatitis C virus within plasma (p. 171).

With regard to claim 13, Cleland *et al.* teach the second biological source cell-free BVDV (p. 171).

With regard to claim 14, Cleland *et al.* use a number of suitable extraction means including solution based and silica matrix methods (p. 171).

With regard to claim 15, Cleland *et al.* teach a first virus HCV and a second virus BVDV.

Cleland *et al.* in view of Gibson *et al.* do not teach a method which comprises a step of combining a compound with the first biological sample prior to the quantification of the nucleic acid in the first biological sample.

Ladner *et al.* teach a method for screening for the effect of a compound on the replication of a nucleic acid, said method comprising steps of combining compounds with a cell culture system (step (a) of claim 10), and after a time quantifying the amount of nucleic acid produced by the cells, and comparing the amount of determined nucleic acid in the treated cell culture to a control that was determined separately in the absence of the compound (as in step (i) of claim 11; p. 1716). With regard to claim 12, Ladner *et al.* teach screening compounds that may affect or interfere with viral life cycle. With regard to claim 16, Ladner *et al.* perform their method in a plurality of wells (p. 1716).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the method for quantifying nucleic acids, particularly HCV nucleic acids, to an assay for screening for compounds that effect replication of HCV nucleic acids, using such techniques as those taught by Ladner *et al.* One would have been motivated to modify the methods taught by Cleland *et al.* in view of Gibson *et al.* in order to have provided a method for screening for compounds that are possible treatment agents against HCV.

Furthermore, one would have been motivated to utilize a method such as the one taught by Ladner *et al.* in order to take advantage of express benefits of such cell-based assays taught by Ladner *et al.* who specifically teach that using a high throughput screening make possible "large-scale screening of diverse chemical libraries in order to identify new classes of inhibitors of HBV replication," stating that with such methodologies 5200 compounds per year could be assayed. Thus, in the absence of an unexpected result, the claimed invention is prima facie obvious.

Conclusion

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Juliet C Switzer
Examiner
Art Unit 1634

May 28, 2004